MEF2C Enhances Dopaminergic Neuron Differentiation of Human Embryonic Stem Cells in a Parkinsonian Rat Model.

Journal: PLoS One

Publication Year: 2011

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PubMed link: 21901155

Funding Grants: MEF2C-Directed Neurogenesis From Human Embryonic Stem Cells

Public Summary:
Human embryonic stem cells (hESCs) can potentially differentiate into any cell type, including dopaminergic neurons to treat Parkinson's disease (PD), but hyperproliferation and tumor formation must be avoided. Accordingly, we use myocyte enhancer factor 2C (MEF2C) as a neurogenic and anti-apoptotic transcription factor to generate neurons from hESC-derived neural stem/progenitor cells (NPCs), thus avoiding hyperproliferation. Here, we report that forced expression of constitutively active MEF2C (MEF2CA) generates significantly greater numbers of neurons with dopaminergic properties in vitro. Conversely, RNAi knockdown of MEF2C in NPCs decreases neuronal differentiation and dendritic length. When we inject MEF2CA-programmed NPCs into 6-hydroxydopamine-lesioned Parkinsonian rats in vivo, the transplanted cells survive well, differentiate into tyrosine hydroxylase-positive neurons, and improve behavioral deficits to a significantly greater degree than non-programmed cells. The enriched generation of dopaminergic neuronal lineages from hESCs by forced expression of MEF2CA in the proper context may prove valuable in cell-based therapy for CNS disorders such as PD.

Scientific Abstract:
Human embryonic stem cells (hESCs) can potentially differentiate into any cell type, including dopaminergic neurons to treat Parkinson's disease (PD), but hyperproliferation and tumor formation must be avoided. Accordingly, we use myocyte enhancer factor 2C (MEF2C) as a neurogenic and anti-apoptotic transcription factor to generate neurons from hESC-derived neural stem/progenitor cells (NPCs), thus avoiding hyperproliferation. Here, we report that forced expression of constitutively active MEF2C (MEF2CA) generates significantly greater numbers of neurons with dopaminergic properties in vitro. Conversely, RNAi knockdown of MEF2C in NPCs decreases neuronal differentiation and dendritic length. When we inject MEF2CA-programmed NPCs into 6-hydroxydopamine-lesioned Parkinsonian rats in vivo, the transplanted cells survive well, differentiate into tyrosine hydroxylase-positive neurons, and improve behavioral deficits to a significantly greater degree than non-programmed cells. The enriched generation of dopaminergic neuronal lineages from hESCs by forced expression of MEF2CA in the proper context may prove valuable in cell-based therapy for CNS disorders such as PD.